Original article **P46**

Compliance with a three-day course of artesunate-mefloquine combination in an area of Thailand with highly multidrug resistant falciparum malaria

Kanungnit Congpuong[1*], Pongwit Bualombai[1],Vick Banmairuroi[2], Kesara Na-Bangchang[2]

[1] Bureau of Vector Borne Disease, Department of Disease Control, Ministry of Public Health, Muang District, Nonthaburi, Thailand,
[2] Graduate Programme in Biomedical Sciences, Faculty of Allied Health Sciences, Thammasat University, Thailand
*Presenting Author

Abstract

The compliance of a three-day course of artesunate (ARS)-mefloquine (MQ) (4 mg/kg body weight ARS once daily for three consecutive days, plus 15 and 10 mg/kg body weight MQ on the first and second days) was evaluated in a total of 240 patients (196 males and 44 females) who were attending the malaria clinics in Mae-Sot, Tak Province and presenting with symptomatic acute uncomplicated *Plasmodium falciparum* malaria. The gametocytocydal anti-malarial drug primaquine (PQ) is administered at the dose of 30 mg (0.6 mg/kg) on the last day. The first dose of the treatment was given to the patients under direct supervision. All patients were given the medication for self-treatment at home and were requested to come back for follow-up on day 3 of the initial treatment. The Kaplan-Meier estimate of the 42-day efficacy rate of this combination regimen was 99.2% (238/240). A three-day combination regimen of ARS-MQ provides excellent patient compliance with good efficacy and tolerability in the treatment of highly multidrug resistance falciparum malaria Based on whole blood MQ and plasma PQ concentrations on day 3 of the initial treatment, compliance with MQ and PQ in this three-day ARS-MQ combination regimen were 96.3% (207/215), and 98.5% (197/200), respectively.

Keywords**:** *Plasmodium falciparum*, artesunate-mefloquine combination, compliance

Introduction

Malaria chemotherapy is under constant threat from the emergence and spread of multidrug resistance of *Plasmodium falciparum.* In Thailand, where multidrug resistant *P. falciparum* is at high level, the National Malaria Control Programme has adopted artesunate (ARS) in combination with mefloquine (MQ) as first-line treatment for uncomplicated falciparum malaria since 1995 (1). The current regimen is a 3-day course of a total dose of 600 mg ARS and 1,250 mg MQ (given as two split doses of 750 and 500 mg). The gametocytocydal anti-malarial drug primaquine (PQ) is administered at the dose of 30 mg (0.6 mg/kg) on the last day. It is believed that this regimen will improve the cure rate and delay anti-malarial drug resistance. The concern is however, patient compliance when applied to field condition. The main purpose of the present study was to investigate patient compliance of the current three-day course of artesunate-mefloquine as first-line treatment for uncomplicated falciparum malaria in Thailand.

Methods

The study was conducted at malaria clinics, Tak Provinces, during March 2008 – February 2009. The study was approved by the Ethics Committee of the Department of Disease Control, Ministry of Public Health of Thailand. A total of 240 patients (196 males and 44 females) presenting with symptomatic acute uncomplicated falciparum malaria (asexual form parasitaemia over 1,000 *per* microliter blood), who had no history of liver and

kidney disease and no previous anti-malarial treatment during the previous four weeks, were recruited into this study. Written informed consents were obtained from all patients before study participation. Patients were treated with a 3-day combination regimen of ARS and MQ. The initial dose of 200 mg ARS (4 tablets; Atlantic Pharmaceutical Company, Thailand) and 750 mg MQ (3 tablets; Atlantic Pharmaceutical Company, Thailand) were given under supervision on the first day (day 0). Then patients were given ARS and MQ tablets for self-treatment at home. The dose regimen on day 2 was 200 mg ARS and 500 mg MQ. On day 3, 200 mg ARS was given with 15 mg (2 tablets; Government Pharmaceutical Organization of Thailand). Patients were requested to return for follow-up in the morning of the third day of treatment (day 3), and on days 7, 14, 21, 28 and 42 or at any time if fever or symptoms suggestive of malaria developed. Blood samples were taken (3 ml) for determination of MQ and PQ concentrations on day 3 to assess patient complaince. MQ and plasma PQ concentrations were measured by high performance liquid chromatography (2, 3).

Results

All patients had a rapid initial response to treatment with parasites cleared from peripheral blood within 3 days of an initial dose of artesunate and mefloquine. The Kaplan-Meier estimate of the 42-day efficacy rate was 99.2% (95% CI 99.0-99.8). No serious adverse event (SAE) was reported during the study. Figure 1 and 2 represent Box and Whisker plot of whole blood MQ and plasma PQ concentrations on day 3 in 215 and 200 cases, respectively. For MQ, the upper, mid and lower lines which represent 1st, 2nd and 3rd quatiles were 1,716, 2,359, and 3,059 ng/ml, respectively. Median (range) concentrations on day 3 were 2,359 (27-10,965) ng/ml, with a 95% confidence interval of 1,977-2,353 ng/ml. There were 10 patients with outlier MQ concentrations (1.5-3 box length apart from the upper or lower limit line). Two had concentrations above the upper limit (10,000 ng/ml), 7 had concentrations below the lower limit (27, 90, 141, 172, 215, 247, 695 ng/ml), and one had undetectable level of MQ (lower than quantification limit). Based on MQ concentrations on day 3, complaince with MQ in this 3-day regimen was 96.3% (207/215). For PQ, the upper, mid and lower lines which represent 1st, 2nd and 3rd quatiles were 1,716, 2,359, and 3,059 ng/ml, respectively. Median (range) concentrations on day 3 were 89 (6-640) ng/ml, with a 95% confidence interval of 75-106 ng/ml. There was no patient with outlier PQ concentrations, but undetecable concentration was observed in three cases. Based on PQ concentrations on day 3, compliance with PQ in this combination regimen was 98.5% (197/200).

Figure 1 Box and Whisker plot of whole blood MQ concentrations on day 3 after the initial treatment. Median, 1st and 3rd quatiles = 2,359, 1,716 and 3,059 ng/ml, respectively. Each individual dots represents the case with outlier concentration below or above 1.5-3 box length

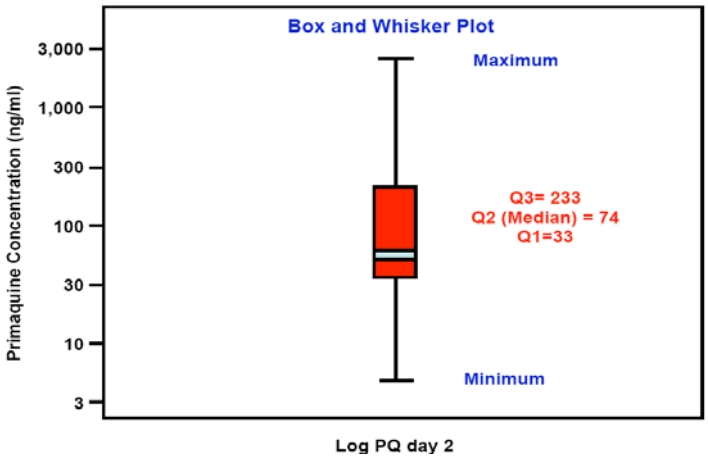

Figure 2 Box and Whisker plot of plasma PQ concentrations on day 3 after the initial treatment. Median, 1st and 3rd quatiles = 33, 74 and 223 ng/ml, respectively. Each individual dots represents the case with outlier concentration below or above 1.5-3 box length

Discussion

The present combination regimen of artesunate-mefloquine was shown to improve the cure rate from approximately 87% with the 2 day course to 96.3% in the same study area (Tak province) during the year 2001 to 2002 (4). As the combination is not a fixed dose regimen, assessment of blood concentration of only one combination partner, *i.e.* mefloquine with long half-life of 14-21 days (5) may not reflect the real full compliance of the combination regimen. Furthermore, since the half-lives of ARS and its active plasma metabolite (dihydroartemisinin) are very short (0.5-2 hr), the drug would have been cleared from blood before 24 hours until patients returned for follow-up on the third day of treatment (day 3). Apart from MQ, plasma concentrations of PQ on day 3 was, therefore, also used as a marker of patient's adherence to the 3-day regimen with the assumption that if patients took primaquine tablets, it was likely that they would have also taken artesunate tablets on the second and third day. Based on mefloquine and primaquine concentrations on day 3 after the intial treatment, patient compliance of as high as 96-98%. This is considered excellent when comparing with compliance to long treatment courses of other regimens, such as a seven-day course of quinine-tetracycine, where prolonged drug administration or a relatively high incidence of cinchonism contributes to about 71.7% compliance in the field trials (6). MQ is a long half-life drug, therefore, whole blood mefloquine levels on day 3 after the initial treatment could be applied for monitoring of compliance to this combination regimen with good accuracy. For PQ on the other hand, plasma concentration on day 3 may not be absolutely a suitable marker for monitoring of compliance to this combination regimen in this field setting as the half-life of primaquine is relatively short (3.7-9.5 hr) (3).

Conclusion

The current first-line treatment three-day combination regimen of ARS-MQ provides excellent patient compliance with good efficacy and tolerability in the treatment of multidrug resistance falciparum malaria in field setting.

Acknowledgements

The study was supported by the Department of Disease Control, Ministry of Public Health, and Commission on Higher Education, Ministry of Education of Thailand.

References

1. Na-Bangchang K, Karbwang J. Current status of malaria chemotherapy and the role of pharmacology in antimalarial drug research and development. Fundam Clin Pharmacol 2009; 23: 387-409.

2. Karbwang J, Molunto P, Na Bangchang K, Bunnag D. Determination of mefloquine in biological fluids using high performance liquid chromatography. Southeast Asian J Trop Med Public Health 1989; 20: 55-60.
3. Na-Bangchang K, Songsaeng W, Thanavibul A, Choroenlarp P, Karbwang J. Pharmacokinetics of primaquine in G6PD deficient and G6PD normal patients with vivax malaria. Trans R Soc Trop Med Hyg 1994; 88: 220-2.
4. Hutagalung R, Paiphun L, Ashley EA, McGready R, Brockman A, Thwai KL, Singhasivanon P, Jelinek T, White NJ, Nosten FH. A randomized trial of artemether-lumefantrine versus mefloquine-artesunate for the treatment of uncomplicated multi-drug resistant *Plasmodium falciparum* on the western border of Thailand. PLoS Med 2005; 2: 330-5.
5. Karbwang J, White NJ. Clinical pharmacokinetics of mefloquine. Clin Pharmacokinet 1990; 19: 264-79.
6. Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, Masngammueng R. Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand. Bull World Health Organ 1998; 76 Suppl 1: 59-66.